<table>
<thead>
<tr>
<th>Supervisor</th>
<th>Project Title</th>
<th>Abstract</th>
<th>Research Theme(s) and CAH3 Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Mahima Swamy</td>
<td>How do T cells maintain quiescence at the intestinal epithelial barrier?</td>
<td>The lining of the gut is constantly exposed to external inputs including food antigens, microbes, and chemicals. Intraepithelial T lymphocytes (IEL) are a specialized subset of immune cells that patrol the single layer of epithelial cells lining the gut. In a normal disease-free state, IEL are resting, and exist in harmony with all these foreign insults. When a pathogen is encountered, however, IEL are able to respond rapidly, either killing the infected or stressed cell, or alerting the rest of the immune system to deal with the situation. We would like to understand how IEL are kept in this resting state, yet can be triggered so rapidly. This is particularly important to understand from a disease-perspective as well, since activated IEL that are left unchecked can drive or aggravate inflammatory bowel diseases such as Crohn’s and Coeliac disease. The project available in my lab is to investigate the contribution of checkpoint immune receptors in keeping IEL in check, using innovative new techniques like high-throughput barcoded phospho-flow cytometry, proximity ligation assays, and in vivo models. These studies will help us to better understand our bodies’ responses to checkpoint blockade therapies in cancer, and how to control inflammation in the gut in inflammatory bowel diseases.</td>
<td></td>
</tr>
<tr>
<td>Dr Gopal Sapkota</td>
<td>Develop efficient CRISPR/Cas9 methods to introduce precise genetic mutations in cells</td>
<td>CRISPR/Cas9 genome editing technology has transformed biomedical research by making rapid gene knockouts and fluorescent tag knockins on individual genes feasible. However, knocking in desired point mutations on individual genes by CRISPR/Cas9 is still challenging and very inefficient. The Sapkota laboratory has developed some CRISPR/Cas9 techniques to improve the efficiency of precise mutation knockins. This project will offer the student to test some novel techniques with the aim of improving these techniques so that we can establish a highly efficient CRISPR/Cas9 methodology for knocking in desired point mutations in different genes. The applications of such a technology will allow researchers to understand the function of enzymes as well as disease mutants in specific cellular contexts.</td>
<td>Cancer Drug Discovery Biotechnology CAH03-01-08 molecular biology, biophysics and biochemistry</td>
</tr>
<tr>
<td>3</td>
<td>Prof Ron Hay</td>
<td>How are SUMO substrates selected for modification</td>
<td>SUMO has diverse roles in cellular physiology that in most cases are mediated by its ability to interact non-covalently with hydrophobic patches of low sequence complexity known as SUMO Interaction Motifs (SIMs). Extensive proteomic analysis has documented the co-ordinate SUMO modification of many components of large nucleoprotein complexes. An emerging mode of action of SUMO is that multiple members of large protein complexes, rather than single proteins, are targeted for modification by the limited number of SUMO E3 ligases. Although the modification of components of the complexes may be sub-stoichiometric this still allows them to interact non-covalently with the more abundant SIM sequences. This serves to increase the stability of the complex such that it attains or retains biological activity. In this situation SUMO modification is acting as a relatively unspecific biological glue. The aim of the project is to determine the molecular basis for the recognition of the nucleoprotein complexes and the SUMO modification of their protein components.</td>
</tr>
<tr>
<td>4</td>
<td>Dr Jens Januschke</td>
<td>Molecular mechanisms of cortical tumour suppressors</td>
<td>Lethal giant larvae (Lgl) is an evolutionarily conserved regulator of cell polarity initially identified in fruit flies. Lgl regulates the actomyosin cytoskeleton and is important to maintain epithelial polarity and integrity. Loss of Lgl occurs in high frequency in human solid malignancies like colon cancer and can drive tumour formation in flies. Importantly, replacing the fly version of Lgl with the Human homolog can substitute all functions in the fly demonstrating functional conservation. The molecular mechanism of action of Lgl has, however, remained mysterious. This project aims at shedding light on the normal function of the tumour suppressor Lgl in fly epithelia and neural stem cells to understand its role in tumorigenesis. The lab has generated new tools allowing the analysis of endogenous Lgl in living tissue as well as the identification of tissue and cell cycle specific binding partners. In this project these tools will be characterised using state-of-the-art confocal live cell microscopy and biochemical approaches as well as CrispR/Cas9 and genetics to unravel the molecular mechanism of Lgl in epithelia and asymmetrically dividing neural stem cells.</td>
</tr>
<tr>
<td>5</td>
<td>Dr Sarah McKim</td>
<td>Regulation of Ideal Plant Architecture in Barley</td>
<td>Plant architecture, or body plan, plays a key role in determining grain yield of crop plants. However, we have little understanding of the molecular genetic basis of architecture in the temperate cereals such as barley (Hordeum vulgare L.), especially in comparison to the warm weather crops such as rice (Oryza sativa). Preliminary data from the McKim lab suggests that a family of microRNA (miRNA) - regulated</td>
</tr>
</tbody>
</table>
transcription factors called the SQUAMOSA PROMOTER BINDING PROTEIN -LIKEs (SPLs) are associated with agronomic traits in barley. This is consistent with work suggesting these factors control ideal plant architecture traits in rice and maize (Jiao et al., 2010; Miura et al., 2010; Wang and Wang, 2015). In this project, the student will test this link through functional characterisation of barley SPLs (HvSPL) by reverse genetics. The student will examine how overexpression and loss of function of HvSPLs in transgenic barley influences architecture and agronomic traits. Through this work, the student will elucidate the functional roles of the SPL transcription factors in barley and their putative contribution to phenotypic variation, revealing potential routes to improved yield through directed breeding. This project will allow scope for the student to master molecular techniques including construct cloning and in situ hybridisation, in addition to glasshouse skills and bioinformatics. The student will train within the unique environment offered by the Division of Plant Sciences, based at the James Hutton Institute (JHI), a centre of world-class expertise in barley.

6 Prof Claire Halpin

Genetic interactions and novel genes that regulate lignin biosynthesis and straw quality in barley

Lignin is a major component of plant cell walls, and has a significant influence on the digestibility and uses of plant biomass. The lignin biosynthesis pathway has been one of the most intensively studied plant metabolic pathways over the past two decades. Nevertheless several fundamental aspects of lignification remain to be understood including aspects of its regulation and its developmental coordination with wider plant metabolism. These are important questions to address given the current world-wide focus on the bio-economy, and the potential of using plant biomass as a renewable feedstock to displace the use of fossil resources and reduce carbon dioxide emissions. We have been using Genome Wide Association Studies (GWAS) across a panel of elite barley cultivars to identify the loci and genes that influence lignin biosynthesis and straw digestibility. We have identified many exciting candidate genes and, in the process, have uncovered networks of interacting genes that cooperate to produce plant secondary cell walls and ensure the production of strong stems that support high grain yield. The networks include many genes of unknown function or that are not appreciated to be involved in cell wall development and we want to discover their specific roles and functions. Some are transcription factors of various classes and others are biosynthetic enzymes. This Masters by Research will help to elucidate how these gene networks function by investigating the roles of a few specific genes. We have large datasets that will facilitate the work including large populations of cultivars with
| 7 | Dr Edgar Huitema | Development of tools suited for the in vivo identification and study of protein Complexes in Phytophthora capsici, required for infection. | Broad host range pathogens, such as the oomycete pathogen Phytophthora capsici, can cause significant disease on a wide range of plants. We have uncovered exciting new evidence demonstrating that P. capsici regulates the expression of its gene complement by sensing its host environment. In order to study the role of P. capsici proteins in dynamic host sensing however, there is a great need for tools that allow the study of both the transcriptional processes and the functional complexes underpinning their regulation, in this pathogen. In this project, we will pursue the following aims:

1. Devise an in vivo protein labelling technique, suited for the identification of functional protein complexes during infection
2. Identify partners of candidate transcriptional regulators, important for virulence
3. Validate and characterise protein complexes, required for infection of plants.

During this project, the researcher will be trained in microbiology, protein chemistry, molecular biology as well as proteomics. Particular attention will be paid to the professional development of researchers on this project by providing career support and active mentoring. | Agritech CAH03-01-08 molecular biology, biophysics and biochemistry |
The aim of this project is to examine the processes by which fungi interact with metals, and rock and mineral-based substrates to understand their significance in biodeterioration of the built environment, and as a potential source of novel biomineral products. Transformations of metals and minerals are central to the biogeochemical activities of microorganisms (1). These processes influence metal speciation, toxicity and mobility, as well as mineral formation or dissolution, and also determine elemental cycles for, e.g. sulfur and phosphorus. As well as being of environmental significance, such processes can have important consequences for human and societal well-being because the same mechanisms can lead to biodeterioration or biocorrosion of metals, rocks, minerals, and mineral-based substrates, e.g. concrete (2). In contrast to this, microbial biofilms may form biomineralized crusts on certain metals, e.g. copper, and stone, mineral and concrete surfaces which may provide bioprotection. Therefore, microbial colonization of surfaces in the built environment may have positive or negative consequences, although there is little knowledge of the mechanisms that may control such effects. Fungi are the most visible and destructive of all colonizing microbiota in the built environment. They are effective at metal bioleaching as they produce many metal-complexing metabolites such as organic acids that can solubilize metals (3). Fungi are also very effective in the biomineralization of metals, i.e. conversion into a solid insoluble biomineral form. Such biomineralization arises from activities of the organisms themselves, such as redox transformations, and metabolic activities where metabolites e.g. oxalate, CO2, may precipitate metals as mineral forms (1-3). Where the formation of new biominerals occurs, there may be formation of novel biominerals (4,5) depending on the elemental composition of the substrate: these may act to form protective rock crusts (6). Many such biominerals are formed in the nanoscale and therefore are of potential industrial interest because of their significant catalytic and reactive properties (7). An understanding of fungal metal and mineral transformations processes is relevant not only to understanding biodeterioration of metal and mineral substrates, but also the formation of novel biomineral products that may have relevance in metal bioremediation or biorecovery. This project will concentrate on a specific aspect within the research theme described and will use an interdisciplinary approach: the student will receive training in geomicrobiology and environmental mineralogy with associated analytical and preparative techniques, including growth and manipulation of
experimental organisms, and techniques including atomic absorption spectrophotometry (AAS), X-ray powder diffraction (XRPD), and advanced light and electron microscopy, X-ray element analysis and mapping. There will also be close collaboration with the Division of Civil Engineering regarding mineralogical analyses.


9 Prof Alessio Ciulli

Bringing proteins together with small molecules

Recent advances from the Ciulli Lab and others have contributed to the establishment of a game-changing new modality of chemical intervention into biological system – one that goes significantly beyond the state-of-the-art. Instead of blocking a target protein with conventional inhibitors, we are now designing and studying “tailored” molecules, bivalent conceptually and in function, that bring proteins together by forming stable and cooperative ternary complexes. We have shown that this key ternary recognition feature allows for fast and effective induce proximity-driven chemistries, specifically protein ubiquitylation and subsequent proteasomal degradation. We are beginning to understand the rules of how to design and study this new class of molecules in order to best trigger specific downstream signaling events, with profound biological consequences and attractive therapeutic potential.

Drug Discovery Cancer
CAH03-01-08 molecular biology, biophysics and biochemistry
Our research in this area takes a multidisciplinary approach including organic and medicinal chemistry and computational tools to design and achieve desired molecules; structural biology and biophysics to study binary and ternary complexes in solution and reveal their structural and dynamic interactions; and chemical biology, biochemistry, proteomics and cell biology to study the cellular impact of our small molecules into relevant cellular systems – for example cancer cells sensitive to the knockdown of the protein target in question. Our science takes advantage of latest technologies and vast expertise available at the School of Life Sciences e.g. within the FingerPrint Proteomics Facility and the Drug Discovery Unit that we have access to. We collaborate with several research groups within the School, including the Divisions of MRC-PPU, GRE, and CSI, to deploy our bivalent molecules to interrogate the biology of targets of interest and to dissect the functional consequences of disrupting the signaling networks in which they are involved.

A one-year Master project would typically fit as part of on-going projects and research interests of the Lab. Importantly; it can be tailored to the student specific interests and motivations. If you are interested in joining the lab and contributing to our science in this exciting new area, to learn more about our work and to discuss potential opportunities, do not hesitate to get in touch with Alessio.

References


| 10 | Dr Miratul Muqit | Uncovering the role of Phosphorylated ubiquitin in health and disease | Ubiquitylation represents a major post-translational modification that controls numerous cellular processes. In the course of our research studies into Parkinson’s disease mechanisms, we discovered that ubiquitin itself can be modified by phosphorylation. In mammalian systems the PINK1 kinase phosphorylates ubiquitin at residue Serine65 (Ser65) and this Ser65-Phospho-ubiquitin functions as a chemical messenger to activate the Parkinson’s ubiquitin ligase, Parkin. Global mass spectrometry screens have provided evidence that ubiquitin can be phosphorylated at other residues in cells and tissues derived from various human cancers. The regulation of these other Phospho-ubiquitin species including the identity of their upstream kinases is unknown and their significance in human disease states unclear. The development of tools is a critical next step and we have recently generated state-of-the-art phospho-specific antibodies against all known ubiquitin phosphorylation sites (Thr7, Thr12, Thr14, Ser20, Ser57, Tyr59, Ser65 and Thr66). The project seeks to determine the biological role of these Phospho-ubiquitin species in cells. Specifically we will deploy these anti-Phospho-ubiquitin antibodies in cells stimulated by diverse stimuli including growth factor stimulation, mitogen activation and DNA-damaging induced stimuli. cellular studies to better understand their regulation in signalling pathways linked to cancer. Where a specific stimulus is identified to induce Phospho-ubiquitin, appropriate follow-up studies will be undertaken to define the regulatory mechanism including the identification of the kinase. The project will also involve a collaboration with the Tayside Biorepository to validate the role of specific Phospho-ubiquitin species in cells and tissues derived from various cancers. |
| 11 | Dr David Murray | Regulation and mechanics in polarity | Membranes and their protein organization are a frontier in our understanding of cell biology. We focus on polarized trafficking as a model to uncover fundamental mechanisms in the organization of structures at membranes. We aim to understand the role of protein complexes including the exocyst. This project seeks to answer mechanistic questions regarding 1) the regulation of protein structural mechanics in polarized trafficking, 2) and the consequences of signalling on this pathway and its organization. Because signalling in polarized trafficking is affected in metastasis of cancer, we position our research for the broadest impact in forming a foundation for drug discovery. We take a reconstitution and synthetic biology approach in combination with the powerful tools available for microscopy. Our philosophy is to address these questions of challenging biology using quantitative methods in a |
hypothesis-driven approach. We are excited to introduce this interdisciplinary research to a highly motivated and ambitious student, who will be expected to have exemplary communication skills and an ability to collaborate. The student will emerge a master in state-of-the-art protein approaches. For any questions on the nature of the proposed research, please do not hesitate to contact me directly dhmurray@dundee.ac.uk or by visiting our website. https://sites.dundee.ac.uk/david-murray-lab/

| 12 | Prof Daan Van Aalten | Biological and molecular mechanisms underlying a new syndromic form of X-linked intellectual disability | Intellectual disability (ID) and concomitant developmental delay are severe neurodevelopmental conditions which affect approximately 1% of the world population. 5% -10% of ID cases are due to mutations in genes located on the X chromosome. One of the genes shown to co-segregate with X-linked intellectual disability (XLID) in twelve patients is the gene ogt. Ogt encodes an essential enzyme, the O-GlcNAc transferase, which catalyses an abundant nucleocytoplasmic post-transcriptional modification O-GlcNAcylation. We have recently described this as a novel syndromic form of XLID (O-GlcNAc Syndrome type I) and are now pursuing four possible hypotheses for underpinning mechanisms, potentially revealing possible future targets for treatment. In your project you would interact with clinicians who have found novel mutations from exome sequencing and use, depending on your interests, a number of possible techniques to study the effects of these mutations. This ranges from biochemical, molecular, cell biological to genetic techniques in model systems ranging from in vitro approaches to stem cells, flies and mice. You will receive expert supervision within the context of an established and well-funded lab. We would aim for your experiments to form the basis of/contribute to a scientific publication. We are looking for hard working, self-driven and independently thinking students. Stop by for an informal chat, contact me on dmfvanaalten@dundee.ac.uk | Drug Discovery Neurodegeneration CAH-03-01-06 Zoology |

| 13 | Dr Greg Findlay | Functions & Applications of a Novel Embryonic Stem Cell Signalling Pathway | The Findlay lab employs cutting-edge technologies to unravel Embryonic Stem (ES) cell signalling networks (Williams et al, Cell Rep 2016, Fernandez-Alonso et al, EMBO Rep 2017; Bustos et al, Cell Rep 2018), culminating in our recent discovery of the ERK5 pathway as an exciting new regulator of ES cell pluripotency. In order to uncover functions of ERK5 in ES cells, this project will deploy global proteomic and phosphoproteomic profiling. Novel ERK5 substrates and transcriptional networks will be characterised using biochemical and ES cell biology approaches. A further aim is to investigate functions of ERK5 in human patient -derived iPS cell maintenance and | Regenerative Medicine CAH03-01-08 molecular biology, biophysics and biochemistry |
lineage-specific differentiation to neurons, cardiomyocytes etc. This research will be undertaken in the MRC Protein Phosphorylation and Ubiquitylation Unit (MRC-PPU), one of the world’s leading centres studying the role of cell signalling in health and disease. Students will have access to state-of-the-art tools to dissect signalling networks, and opportunity for interaction with three major Pharmaceutical companies that support the MRC-PPU via the Division of Signal Transduction Therapy. The Findlay lab is also affiliated with the Division of Cell and Developmental Biology, which comprises world experts in stem cell research.

| 14 | Dr Davide Bulgarelli | A synthetic community approach to define the genetic mechanisms underpinning plant-microbiota interactions in the rhizosphere | The proposed project will be integrated into our long-term efforts to reconstruct synthetic communities of the microbiota populating the rhizosphere, the thin layer of soil adhering to plant roots, and determine their presumed contributions to plant growth and health, using Barley (Hordeum vulgare) as an experimental model. In particular, the student will focus on subset of bacteria whose recruitment at the barley root-soil interface is regulated by the host plant. S/he will use a recolonization assay we recently established in our lab to define the impact of these bacteria on aboveground and root biomass (proxies for plant growth). In parallel, the student will define the host range of these bacteria by performing recolonization assays with different barley genotypes and monitoring bacterial proliferation in the rhizosphere using both cultivation-dependent (e.g., colony counts) and-independent (e.g., PCR-based biomarkers) approaches. Finally, the student will subject selected bacteria to whole-genome sequencing to reconstruct their metabolic potential. In the long term, the information gathered in this project will be critical for the rational development of microbial inoculants for agriculture.

Further reading:
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| Prof Mark Field | Development of novel therapeutics against parasitic disease | Many drugs that are developed experimentally against pathogens fail, and one of the most common causes is due to an inability to efficiently enter the cell. This can be a result of acquisition of resistance (AMR) or of an intrinsic inability to cross the plasma membrane. This project will investigate the use of camelid nano-bodies (mini-immunoglobulins) as a means to provide access to the cell interior in the African trypanosome. We have developed a panel of nano-bodies which bind to surface proteins of the trypanosomes, and which we believe will be internalised. Uptake of these nano-bodies coupled to novel drug compounds has the potential to provide a new approach to drug therapy against trypanosomes and related parasites. The project will involve high resolution imaging, protein chemistry and drug design and will provide an excellent training in the burgeoning area of immunotherapeutics. Interested candidates can contact Prof Field at mfield@mac.com | Antimicrobial Resistance  
Drug Discovery  
Immunotherapy  
CAH02-03-10) biomedical sciences (non-specific) |
| (1) Prof Kim Dale  
(2) Dr Jens Januschke | Does CDK1 regulate NICD turnover in a cell cycle dependant manner in Drosophila Melanogaster? | Notch is one of the major highly conserved signalling pathways that regulate cell-cell communication which involves gene regulation mechanisms that control multiple processes during development and adult life, including cell fate specification within progenitors. Upon extracellular ligand binding, Notch transmembrane receptors are cleaved, releasing the intracellular domain (NICD) that translocates to the nucleus to regulate expression of specific developmental gene cohorts. NICD is highly labile, and phosphorylation-dependent turnover acts to restrict Notch signalling. Most canonical Notch activity relies on this regulation of NICD turnover. Moreover, aberrant NICD turnover contributes to numerous cancers and diseases. Despite the multiple impacts of NICD turnover in both development and disease, the molecular mechanism regulating this turnover remains largely uncharacterised. The stability of NICD and therefore duration of the Notch signal is regulated by phosphorylation of the C-Terminal PEST domain which leads to subsequent recruitment of FBXW7, F-Box and WD Repeat Domain Containing 7, (a key component of the SCFSel10/FBXW7 E3 ubiquitin ligase complex). Ultimately, this leads NICD to ubiquitylation and proteasomal degradation. However, the molecular details of NICD degradation mediated by FBXW7 are not well understood. | Cancer  
Neurodegeneration  
Regenerative Medicine (CAH03-01-08) molecular biology, biophysics and biochemistry |
We recently identified a highly conserved site crucial for NICD recognition by the SCF E3 ligase, which targets NICD for degradation. We demonstrate both CDK1 and CDK2 can phosphorylate NICD in the domain where this crucial residue lies and that NICD levels vary in a cell cycle-dependent manner. Inhibiting CDK1 or CDK2 activity increases NICD levels both \textit{in vitro} in a number of human cell lines and \textit{in vivo} during early vertebrate development in the presomitic mesoderm where Notch plays a critical role on the progressive formation of the segmented body axis.

This project will investigate whether this regulatory system is conserved in another \textit{in vivo} context, namely in the Fruit fly Drosophila melanogaster where Notch was first identified in 1919. The lab of Dr. Jens Januschke has developed a novel tool with which to inhibit CDK1 function – through the generation of an analogue sensitive kinase.

**Aims:**

1. Is Notch turnover sensitive to the CDK1 analogue sensitive kinase in Drosophila melanogaster embryonic development?
2. Is NICD turnover correlated with the cell cycle in Drosophila melanogaster embryonic development?
3. What is the functional consequence of interfering with Notch turnover during Drosophila melanogaster embryonic development?

<table>
<thead>
<tr>
<th>17</th>
<th>Prof Kim Dale</th>
</tr>
</thead>
</table>

Does increasing stability of Notch affect formation of the segmented body axis?

Notch is one of the major highly conserved signalling pathways that regulate cell-cell communication which involves gene regulation mechanisms that control multiple processes during development and adult life, including cell fate specification within progenitors. Upon extracellular ligand binding, Notch transmembrane receptors are cleaved, releasing the intracellular domain (NICD) that translocates to the nucleus to regulate expression of specific developmental gene cohorts. NICD is highly labile, and phosphorylation-dependent turnover acts to restrict Notch signalling.

Most canonical Notch activity relies on this regulation of NICD turnover. Moreover, aberrant NICD turnover contributes to numerous cancers and diseases. Despite the multiple impacts of NICD turnover in both development and disease, the molecular mechanism regulating this turnover remains largely uncharacterised. The stability of NICD and therefore duration of the Notch signal is regulated by phosphorylation of the C-Terminal PEST domain which leads to subsequent recruitment of FBXW7, F-Box and WD Repeat Domain Containing 7, (a key component of the SCF\textit{Sel10/FBXW7} E3 ubiquitin

Cancer Regenerative Medicine
CAH03-01-01 biosciences (non-specific)
ligase complex). Ultimately, this leads NICD to ubiquitylation and proteasomal degradation. However, the molecular details of NICD degradation mediated by FBXW7 are not well understood.

We recently identified a highly conserved site crucial for NICD recognition by the SCF E3 ligase, which targets NICD for degradation, in *in vitro* assays. We have used Crispr/CAS9 gene editing technology in mouse embryonic stem cells and human iPS cells to knockin a version of Notch 1 with a point mutation in the residue required for recognition by the SCF E3 ligase.

During early vertebrate development Notch plays a critical role on the progressive formation of the segmented body axis. This process is called somitogenesis and comprises the progressive periodic formation of segments called somites from a tissue called the presomitic mesoderm. The periodicity of the process is regulated by a molecular oscillator acting in the cells of the presomitic medoderm that drives periodic expression of so called clock genes, most of which are Notch target genes.

This project will investigate whether a point mutation in a highly conserved site crucial for affects NICD recognition by the SCF E3 ligase affects the ability of mouse embryonic stem cells and human iPS cells to differentiate into presomitic mesoderm cells and if this has any effect on the periodic expression of the clock genes.

**Aims:**

1. Does the S2513A Notch1 mutation render NICD non phosphorylatable?
2. Does the S2513A Notch1 mutation affect levels of NICD through inhibiting the interaction with the SCF E3 ligase at endogenous levels?
3. Does the S2513A Notch1 mutation affect the ability of mouse embryonic stem cells and human iPS cells to differentiate into presomitic mesoderm cells?
4. Does the S2513A Notch1 mutation affect the dynamic oscillatory expression of clock genes in the presomitic mesoderm?

| 18 | Dr Jorunn Bos | Mechanisms underlying aphid effector virulence activity | Pests and diseases are a major threat to food security with losses ranging between 20-40%. Aphids are one of the most devastating insect pests, globally. These insects form a close association with their host and use specialized mouthparts (stylets), to probe leaf tissue and feed on the phloem over prolonged periods of time. Upon puncturing the leaf epidermis, the stylets follow a mainly extracellular route through the different cell layers | Agritech (CAH03-01-05) plant sciences |
to reach the phloem, and puncture cells along the pathway. During probing and feeding, saliva is secreted, which is rich in proteins and small molecules that function as effectors in reprogramming host processes underlying susceptibility. Functional characterization studies have implicated several effectors in aphid virulence, indicating that they are important players in plant-aphid interactions. In our bid to attribute function to an increasing number of candidate effectors, the identification of their cellular host targets represents a critical step. We previously initiated an aphid effector host target identification approach to determine the role of effectors in manipulating host cell processes. This led to the identification of 6 different effector-host protein interactions. This project will focus on the characterization of one of these interactions in more detail to understand the role of aphid-host protein interactions in host susceptibility.

The student will use molecular biology and biochemistry approaches, such as mutagenesis, Gateway cloning and co-immunoprecipitation assays, to determine protein regions/amino acids required for protein-protein interactions. In addition, *in planta* functional assays will be used to explore the link between effector-host protein interactions and susceptibility. These assays will include *in planta* overexpression and silencing of host proteins as well as aphid effectors, and aphid performance assays. The project will help us better understand how aphids are able to manipulate the host to their own benefit, and generate novel insight into the molecular co-evolution of plant-herbivorous insect interactions.

| 19 | Dr Adrien Rousseau | Signalling pathways controlling protein degradation upon stress | Increasing evidence shows that alterations and mutations in the UPS give rise to various human diseases, such as cancer and neurodegenerative disorders. Our interest is to understand how the activity of the ubiquitin-proteasome system is regulated in cells so that accumulation of unfolded, misfolded, or damaged proteins can be cleared before they become deleterious. We recently reported that proteasomal degradation is regulated upon proteotoxic stresses in a phosphorylation-dependent manner (Rousseau and Bertolotti, 2016). The new project will focus on how protein phosphorylation events regulate protein homeostasis and cell survival. An additional project consists in developing new tools to characterize how proteasome homeostasis is regulated in cells, | Neurodegeneration CAH3-01-02 - Biology, non-specific |
and to use these tools to identify new regulators and drugs modulating proteasomal degradation. Both yeast and mammalian systems will be used for this project.

| 20 | Dr Esther Sammler | LRRK2 kinase pathway activation during infection | LRRK2 functions as a kinase and hyperactivating mutations cause 1-2% of all cases of Parkinson’s disease. LRRK2 is highly expressed in immune cells and LRRK2 signalling appears to play a role in immune defence mechanisms. In fact, increased LRRK2 activity may protect against opportunistic infections, but later in life, increase the risk of developing Parkinson’s disease, a concept known as antagonistic pleiotropy. This project plans to explore LRRK2 kinase pathway activation throughout the course of an infect exacerbation in patients with chronic lung disease. For this, neutrophils from peripheral blood and sputum will be isolated at up to 3 timepoints: at the time of presentation with an acute infect exacerbation (1), at the end of a course a course of antibiotics / infect resolution (2) as well as once in between (3). Neutrophils will be processed and analysed by multiplex quantitative Western blotting for LRRK2 controlled phosphorylation of its endogenous substrate Rab10 which is a proxy for LRRK2 kinase activation status (Biochem J. 2018 Jan 2;475(1):23-44. doi: 10.1042/BCJ20170803.). This is an exciting translational research opportunity. The student would work with leading clinicians and research nurses at the Ninewells site – who will facilitate recruitment of patients and bio-sample collection – while being mainly based at the MRC Protein Phosphorylation and Ubiquitylation Unit. |

| 21 | Dr Yogesh Kulathu | Deciphering the ubiquitin codes that regulate protein degradation | Ubiquitin signalling, which involves the posttranslational modification (PTM) of proteins with ubiquitin, regulates almost every aspect of eukaryotic biology. This versatility is possible because proteins can be modified with different types of ubiquitin codes resulting in distinct functional outcomes. An indispensable role for ubiquitylation is to serve as a signal for the degradation of misfolded and damaged proteins. In addition to degradation, ubiquitin modifications can serve as distinct signals to facilitate intracellular communication. The cellular machinery therefore has to read the different ubiquitin codes in order to ensure that the appropriate response is produced. Further, these codes have to be erased once the functional outcome is produced, a process carried out by a class of enzymes known as Deubiquitinases. In the lab we study these processes, using a range of techniques including biochemical approaches, proteomics, structural biology | Translational research  
Infection  
Neurodegeneration  
CAH03-01-01 biosciences  
Cancer  
Neurodegeneration  
CAH-03-01-08 molecular biology, biophysics and biochemistry |
and mouse models to elucidate new layers of control in protein degradation. This research is fundamental to our understanding of cell biology in health, and is important, as failures in protein degradation underly many diseases especially age-related diseases such as Alzheimer’s and Parkinson’s disease.

We are looking for an enthusiastic student to join the group to study how protein degradation is regulated by the ubiquitin system. Your PhD will build upon tools, reagents and models we have recently established in the lab. Working on an independent project, you will have the opportunity to learn and apply different approaches ranging from biochemistry, cell biology, genetic screens and state-of-the-art proteomics methods to understand at the molecular level how aberrant proteins are degraded, the ubiquitin signals involved, how they are decoded and how this process is regulated. This project will provide the opportunity to improve our understanding of one of the most fundamental processes in the cell.

|   | Prof Tom Owen-Hughes | Investigating the tumor suppressor functions of chromatin remodelling | One of the unanticipated outcomes of population based genome sequencing has been the finding that genes involved in the regulation of many genes are mutated at high frequency in tissue specific cancers. This is the case for SWI/SNF –related chromatin remodelling enzymes which are mutated in about 20% of all tumors and at higher frequencies in cancers of specific tissues. To understand how these genes function we have engineered cell lines in which specific subunits of these enzymes can be degraded rapidly and specifically. In this project, chromatin immunoprecipitation and RNA sequencing will be used to gain insight into how these complexes function. In the long run characterising these pathways will provide new routes for the development of cancer therapies. | Artificial Intelligence  
Cancer  
Drug Discovery  
Immunotherapy  
(CAH02-03-10) biomedical sciences (non-specific) |
|---|---|---|---|---|
| 22 | Dr Sarah McKim | Jasmonate control of barley development | From the earliest farmers to modern plant breeders, humans have continually modified the body plan of cereals, sometimes drastically, to generate higher grain yields. Excitingly, recent work in the McKim lab suggests that architecture in barley, a key global crop, is controlled by jasmonate, a classic plant stress/defense hormone (Patil et al., 2019). However, we don’t know how other pathways controlling architecture interact | AgriTech  
CAH03-01-05 plant sciences |
with jasmonate or whether environmental cues use jasmonate to control barley development.
In this project, you will use genetic analyses and physiological experiments to understand how the jasmonate pathway controls development in barley. You will also investigate how jasmonate may act as a long-range signal to control plant architecture and how to learn how jasmonate may alter susceptibility to pathogens and pests during plant development. Taken together, you will reveal the developmental roles of jasmonate in barley about which almost nothing is known, and advance our understanding of interactions which influence stem elongation and flowering.

Students with a passion for research who are motivated by a desire to improve our food security are the best fit for this project. The student will also benefit from a unique training environment offered by the Division of Plant Sciences, based at the James Hutton Institute (JHI), one of the best centres in the world to study cereals, and the site of the new International Barley Hub (2).

(2) http://www.barleyhub.org/

| 24 | Dr Gabriel Sollberger | Study the difference of inflammasome pathways in human neutrophils and macrophages | The innate immune system uses a broad variety of sensors to detect cues of infections (pathogen-associated molecular patterns, PAMPs) or signs of cell and tissue damage (danger-associated molecular patterns, DAMPs). Recognition of PAMPs and DAMPs usually results in the production and release of pro-inflammatory mediators. Often, the activation of sensors and their downstream effectors also results in lysis and death of the activated cell, which makes it paramount that this activation is tightly controlled. If control mechanisms fail and excessive immune cell death occurs, this has detrimental consequences for the host, such as septic shock or the development of autoimmune diseases. An example of such processes is activation of inflammasomes. Inflammasomes are multiprotein complexes, which – upon sensing of PAMPs or DAMPs – induce the release of IL-1β, a very potent pro-inflammatory cytokine (1). Inflammasomes are mostly studied in macrophages and much less is known in the most abundant human immune cell, the neutrophil. Neutrophils, rather than secreting IL-1β, undergo a special form of cell death when activated, they form neutrophil extracellular traps (NETs). NETs consist of DNA and protein; dying neutrophils expel them as web-like structures and thereby catch extracellular pathogens (2). Remarkably, we previously | Antimicrobial Resistance (AMR) Immunotherapy CAH02-03-10 biomedical sciences (non-specific) |
found that there is crosstalk between the molecular machinery mediating
inflammasome activation in macrophages and NET formation in neutrophils (3).

This project therefore aims to **study, what the differences are between inflammasomes in neutrophils and macrophages** and **if these differences affect the outcome of infections and inflammasome or NET-driven pathology**. The project will use human cells and a combination of cell biological and genetic techniques to answer these important immunological questions from a mechanistic perspective. It will thereby contribute to our understanding of inflammation, infection and sterile pathologies and help to identify possible new drug targets to tackle such pathologies.


| 25 | Dr Federico Pelisch | Identification and role of key phosphorylation events during oocyte meio | Formation of a diploid embryo requires that sperm and egg contribute exactly one copy of each chromosome. The cell division in charge of reducing ploidy of the genome is meiosis. Female meiosis is particularly error-prone, leading to chromosomally abnormalembrayos that account for >10% of human pregnancies and, for women nearing menopause, the incidence may exceed 50%. Therefore, understanding the molecular events that guarantee proper chromosome segregation during female meiosis is of paramount relevance. In spite of this, and in contrast to mitosis, we still do not have a molecular understanding of the events regulating meiotic chromosome segregation. Our recent work has focused on chromosome segregation during oocyte meiosis using the nematode C. elegans as a model organism, which provides an excellent system for studying meiosis. We are interested in the signalling networks that guarantee that every single protein performing a function during meiosis is present at the right place, in the right time. In many instances these signals are in the form of post-translational protein modifications (PTMs) and we focus on two of these: | Cancer | CAH02-03-10 biomedical sciences (non-specific) |
phosphorylation and sumoylation. Within each modification pathway, there is a high level of coordination between the enzymes that add the modifications onto substrates and the enzymes that remove the modification from. Additionally, there is a high level of coordination between the pathways. Our evidence suggests that sumoylation and phosphorylation do not act in isolation during meiosis. In order to understand the mechanism involved in accurate meiotic chromosome segregation, we will employ state-of-the-art mass spectrometry to identify key sumoylation and phosphorylation events in vivo during meiosis. Furthermore, we aim at developing a method to establish stage-specific (pre-anaphase and anaphase) meiosis I sumo-and phospho-proteomes. Once identified, we will study the roles that these sites play during meiosis in vivo though time-lapse microscopy, with high spatial and temporal resolution.

<table>
<thead>
<tr>
<th>26</th>
<th>Dr Piers Hemsley</th>
<th>Greasing protein function – how is post-translational protein S-acylation regulated in plants?</th>
</tr>
</thead>
</table>
|  |  | Protein S-acylation is a poorly understood fatty acid based post-translational modification of proteins, yet affects half of all membrane proteins and plays a role in every membrane associated process in plants. We have shown the S-acylation is key to fundamental aspects of plant biology including cellulose synthase function, pathogen perception, hormone signalling and water homeostasis during environmental stress. Knowledge of S-acylation is therefore crucial to understanding the basic biology of plant function and is key to many aspects of plant biology required for mitigating climate change, water shortages or boosting crop yield. 
  
We recently found that S-acylation state can change in response to stimuli, is enzymatic and has profound effects on protein function. This places S-acylation alongside phosphorylation and ubiquitination in terms of regulatory importance but the mechanism underlying how changes in protein S-acylation state occurs is still unclear. We have identified enzymes that add S-acyl groups to proteins and have a shortlist of candidate de-S-acylating enzymes able to remove S-acyl groups; the basis for a regulatory cycle therefore exists. Using model S-acylated proteins involved in pathogen perception, hormone responses and water stress mitigation this project aims to 1) validate these enzyme candidates and 2) develop strategies to monitor dynamic S-acylation of proteins in plants. |
|  |  | 1. Validation of candidate de-S-acylating enzymes |
|  | Agritech CAH03-01-05 plant sciences |
|   | Prof Kim Dale | The role of the CCR4-NOT complex in somite segmentation | During early embryogenesis the somites are formed during a process called segmentation. The somites will go on to form the bones and muscles of the skeleton. This a highly regulated process where somites bud off the rostral end of the presomitic mesoderm (PSM) at regular intervals. The timing of the process is thought to be regulated by a molecular oscillator, called the segmentation clock, that drives cyclic gene expression across the PSM with a periodicity that matches somite formation. The so called- clock genes belong to three signalling pathways; Notch, FGF and Wnt all of which are essential for development and many diseases, including a variety of cancers, are caused by abnormal signalling of three pathways. Quite a lot of research has been done on how the oscillating expression of the clock genes is switched on, however far less is known about how they are switched off and how the corresponding mRNAs and proteins are degraded at the |

27 | Cancer Regenerative Medicine CAH03-01-08 molecular biology, biophysics and biochemistry |
correct times. This project would investigate the role of translation efficiency and mRNA stability in the regulation of the segmentation clock. A few papers show that the 3’ untranslated regions (UTRs) of some of the oscillating genes are required for correct segmentation patterns. UTRs of many mRNAs are critical for correct localisation, translation and mRNA stability. In a recent paper the critical role of the CCR4-NOT complex in the segmentation in zebrafish embryos was established. This complex can both repress translation and destabilise the mRNA via deadenylation. Research on the role of mRNA translation and stability in the regulation of the circadian clock shows that only some mRNAs encoding for oscillating proteins oscillate themselves suggesting that they are regulated at the level of translation efficiency. It would be interesting to investigate by which mechanism the segmentation clock genes are regulated and what the role would be of e.g. mRNA translation and stability, the CCR4-NOT complex, RNA binding proteins, miRNAs, long non coding RNAs and/or RNA modifications.

| No. | Dr Kasper Rasmussen | The epigenetic basis of blood diseases | The epigenetic mark of DNA methylation is established by DNMT (DNA methyltransferase) enzymes and has been shown to correlate with transcriptional states and influence cell identity and tumorigenesis in mammalian cells. The recent discovery that TET (Ten-Eleven-Translocation) enzymes produce 5-hydromethylcytosine (5hmC), 5-formylcytosine (5fC), 5-carboxycytosine (5caC) and mediate passive and active DNA demethylation in the genome has opened a new avenue to understand how DNA methylation dynamics affect transcriptional programs (Rasmussen and Helin, 2016). Mutations in TET2 and DNMT3A are frequently found (~10-50% of patients) in a wide range of blood diseases, including Acute Myeloid Leukemia (AML) and Myelodysplastic syndrome (MDS). However, the downstream events that cause hematopoietic stem cell to expand and transform following the occurrence of these mutations are currently unknown. The 1-year Master Project will be aligned with on-going projects in the lab to characterize the effect of aberrant DNA methylation on gene expression and link this to haematological diseases. Students with an interest in epigenetics and gene regulation are most welcome to contact Kasper on k.d.rasmussen@dundee.ac.uk and visit the lab for an informal talk about detailed projects. | Cancer CAH03-01-01 biosciences (non-specific) |
| Dr Leeanne McGurk | ADP-ribosylation in the aging nervous system | ADP-ribosylation is a fundamental posttranslational modification where ADP-ribose is linked on to target proteins by ADP-ribose transferases and removed by the ADP-ribose hydrolases. Emerging data implicate ADP-ribosylation in maintaining the health of the nervous system; mutations in the genes that encode the enzymes that reverse ADP-ribosylation cause neurodegenerative disease in humans and pharmacological inhibition of the ADP-ribose transferases is therapeutically beneficial in various cellular and animal models of human neurodegenerative diseases such as stroke, Parkinson’s disease and motor neuron disease (reviewed in 1). This suggests that ADP-ribosylation regulates key proteins involved in brain aging, however what these proteins are and how they are regulated by ADP-ribosylation is unknown. To elucidate the proteins and underlying mechanisms that regulate brain aging, the student will use an interdisciplinary approach that combines genetics of the fruit fly with molecular and cellular approaches to determine the role of nuclear ADP-ribosylation in the aging and diseased nervous system of the fly (AIM1) and in human iPSC-derived neurons (AIM2). At the end of this project the student will have identified novel aspects of ADP-ribosylation in the normal and diseased nervous system. |

**Background reading**

| 30 | Prof Kevin Read | Assessment of plated cryopreserved hepatocytes as a tool to accurately determine the intrinsic clearance of low metabolism compounds | Reducing the metabolic clearance of new chemical entities is important in drug discovery projects helping to reduce dose, improve exposure and prolong the half-life of new chemical entities (NCE’s). Primary hepatocytes in suspension are routinely used to assess intrinsic clearance and predict in vivo clearance, however incubation times are limited to <4 hours, which is not long enough to accurately determine the metabolic stability of slowly metabolised compounds. It is important to be able to generate accurate *in vitro* intrinsic clearance when predicting *in vivo* human clearance so an alternative assay is necessary for slow/poorly metabolised NCE’s. Plateable ‘metabolism qualified’ cryopreserved human hepatocytes are a cost-effective, commercially available *in vitro* tool that maintain *in vivo*-like enzyme expression levels and cell morphology. These cells can be cultured for more prolonged timescales and a more accurate evaluation of metabolic stability can be determined. Plateable human hepatocytes have previously been demonstrated to predict well with observed *in vivo* human hepatic clearance to within 3-fold in 78% of the compounds tested. Differing culture media and supplements have also shown to have a significant effect upon culture time and metabolic enzyme activity over the course of the experiment thereby improving the precision of human *in vivo* predictions.

Proof-of-concept will initially be performed on a test set of low intrinsic clearance compounds with available *in vivo* clearance data. A variety of experimental conditions will be explored to validate this as an accurate tool for delivering better prediction of slow/low intrinsic clearance NCE’s within the Drug Discovery Unit. | Drug Discovery CAH02-03-10 biomedical sciences (non-specific) |